

**REMARKS**

Claims 69-95 and 115-147 are currently pending in this application. Claims 91-95 and 147 have been canceled, without admission and without prejudice to Applicants' right to pursue those canceled claims in either this or other (*e.g.*, related) patent applications. Claims 115-117 and 123 have been amended, pursuant to the Examiner's suggestions, to correct minor claim informalities. Hence, claims 69-90 and 115-146 will remain pending upon entry of these amendments.

The specification has also been amended to correct certain informalities and pursuant to the Examiner's suggestions. In particular, the Title of the Invention has been amended to the Title suggested at page 3 of the Office Action. The paragraph starting at line 8 on page 5 of the specification has also been amended, to delete the sentence fragment at the end of that paragraph (*i.e.*, on lines 16-17 of page 5). Finally, a Substitute Abstract of the Disclosure is submitted herewith, which avoids the use of "novel," as requested in the Office Action.

No new matter has been introduced by these amendments. Therefore, entry and consideration of the amendments are respectfully requested.

**I. The Substitute Drawings**

Applicants note, with appreciation, that the Substitute Drawings submitted on March 28, 2003 have been accepted for this application. Accordingly, Applicants understand that it is not necessary to submit formal drawings for this application.

**II. The Claim For Domestic Priority Under 35 U.S.C. § 119(e)**

The Office Action acknowledges this application's claim for priority to U.S. provisional application Serial No. 60/150,452 filed on August 24, 1999 (hereinafter referred to as "the provisional application"). However, the Office Action indicates that the provisional application does not contain adequate support for the pending claims of this application. Consequently, the pending claims have not been accorded the benefit of the provisional application's earlier filing date. In response, Applicants respectfully submit that the pending claims are supported in the provisional application and should therefore be accorded benefit of that application's earlier filing date.

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In particular, the provisional application describes the isolation of several hybridomas that specifically bind human CTLA-4. See, for example, on page 58, lines 8-9 of the provisional application as filed. See also on page 7, lines 21-28 which lists many of these specific hybridomas. The provisional application also describes assays by which the antibodies' ability to inhibit B-7 ligand to human CTLA-4 is tested, and many of the antibodies are reported to "strongly inhibit CTLA4 binding to the B7 ligand." See, in the provisional application, at page 58, lines 15-16. Binding kinetics of the antibodies are also reported, and are shown to be equal to or greater than  $10^9 \text{ M}^{-1}$ .

The Office Action alleges that the provisional application does not describe any human antibodies to CTLA-4 wherein the heavy or light chains are limited to any specific sequences or families. Yet, among the hybridomas described in the provisional application are ones referred to as 10D1, 4B6 and 11E8. See, for example, in the table on page 58 of the provisional application. See also, the list of hybridomas recited in the provisional application on page 7, lines 21-27. Moreover, heavy and light chain variable domain sequences of at least one antibody (10D1) are disclosed in the provisional application. See, in particular, on page 59, lines 21-22 and the nucleotide sequences set forth in SEQ ID NOS:1-2 on pages 61 of the provisional application. While the provisional application may not disclose specific sequences and/or V gene sequences *in haec verba*, these limitations are clearly inherent features of the antibodies and hybridomas described in that application.

The test for sufficiency of support in a parent application is not whether the limitation is disclosed *in haec verba* in the priority application, but "whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." See, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-1564, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). As explained above, the provisional application clearly establishes that, as of its filing date, Applicants were in possession of the antibodies now claimed in this application. Hence, the pending claims should be accorded benefit of the provisional applications earlier filing date.

**III. The Objections to the Specification Have Been Obviated**

The Office Action notes that there are certain informalities in the specification that should be corrected. In particular, the Examiner has suggested that the Title of Invention be changed to -- HUMAN CTLA-4 ANTIBODIES --. The Examiner has also noted that there is an improper sentence fragment, on page 5, lines 16-17 of the specification. Finally, the Examiner has objected to the Abstract of the Disclosure, and requests a new Abstract that avoids use of the word "novel."

The specification has been amended, *supra*, to address each of these informalities. In particular, the Title of Invention has been changed to that proposed by the Examiner. Also, the paragraph starting at line 8 on page 5 of the specification has been amended to remove the sentence fragment. Finally, a Substitute Abstract of the Disclosure is submitted herewith at **Tab 1**. As requested by the Examiner, this Substitute Abstract does not contain the word "novel" but is otherwise identical to the original Abstract of the Disclosure filed with this application.

It is believed that these amendments obviate the Examiner's objections to the specification. Accordingly, Applicants respectfully request that these objections be withdrawn.

**IV. The Objections to the Pending Claims Have Been Obviated**

Applicants note, with appreciation, that the Examiner has found the subject matter of claims 122-123 and 115-117 to be allowable. However, the Examiner has objected to certain informalities in these claims. In particular, the Examiner has noted that claims 122 and 123 are identical and therefore redundant. Also, claims 115-117 actually specify "the amino acid sequence set forth in SEQ ID NOS" (*pl.*) when only a single SEQ ID NO. is recited.

Accordingly, claims 123 and 115-117 have been amended pursuant to correct these informalities. In particular, claim 123 has been amended to specify a binding affinity of  $10^9 \text{ M}^{-1}$ , rather than  $10^8 \text{ M}^{-1}$ . Hence, claims 123 is no longer duplicative of claim 122. Also, claims 115-117 have been amended as suggested by the Examiner, so that they only specify a single "SEQ ID NO". It is believed that these amendments obviate the Examiner's objections to the pending claims. The withdrawal of those claim objections is therefore respectfully requested.

**V. The Rejections Under 35 U.S.C. § 112,  
First Paragraph, Should Be Withdrawn**

Claims 69-95, 125-129 and 134-147 have been rejected under the first paragraph of 35 U.S.C. § 112, as failing to comply with the written description requirement. In particular, the Office Action, while acknowledging that there is adequate written description of antibodies encoded by particular combinations of heavy and light chain variable genes, alleges that there is not adequate written description of antibodies defined by a particular heavy *or* light chain variable gene. In addition, the Office Action also alleges that functional properties recited in claims 92-95, 125-129 are described only for a single antibody (specifically, the antibody referred to as 10D1) which, according to the Office Action, is not adequate to support the claimed subgenus of antibody. The Office Action further indicates that this rejection constitutes a rejection for new matter, and requires Applicants to cancel the rejected claims.

At the outset, Applicants respectfully point out that claims 91-95 and 147 have been canceled in the above amendments, without prejudice or admission. Hence, of the claims rejected under the first paragraph of 35 U.S.C. § 112, only claims 69-90, 125-129 and 134-146 will remain pending upon the entry of these amendments. Applicants respectfully decline to cancel these remaining claims, and instead submit that they are all adequately described in the present application as filed. In particular, Applicants respectfully direct the Examiner's attention to the definition of "antibody" set forth in the present application, starting at page 18, line 10. This definition makes it clear that the antibodies of this invention are not just limited to "intact" antibodies having particular combinations of V<sub>H</sub> and V<sub>L</sub> sequences. Rather, the definition explains that antibodies of the invention can also be, *e.g.*, Fd fragments (*i.e.*, fragments consisting of V<sub>H</sub> and C<sub>H1</sub> domains), dAb fragments (*i.e.*, fragments consisting of a V<sub>H</sub> domain) or isolated complementarity determining regions, to name a few. See, in particular, at page 18, lines 29-32. Hence, contrary to what is stated in the Office Action, the present application actually does describe human antibodies which bind CTLA-4 and utilize either a V<sub>H</sub> or a V<sub>L</sub> region encoded by a particular gene.

With respect to the rejection of claims 125-129 and 134-138, the Office Action indicates that there is not adequate written description because the specification only describes one antibody with the functional properties recited in these claims – namely, the antibody 10D1. As Applicants understand this rejection, therefore, the Examiner does not consider the antibody 10D1 to be

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representative of the genus of antibodies with the recited functional properties (*i.e.*, inhibiting B7 ligand, not cross-reacting with other tissues, *etc.*).

The written description requirement for a claimed genus can be satisfied through sufficient description of a “representative number of species” – *i.e.*, where the species which are adequately described are representative of the entire genus. Yet, the requirement for a “representative number of species” does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Rather, what constitutes a “representative number” of species is actually an inverse function of skill and knowledge in the art. Consequently, there can be situations where one species adequately supports a genus. *In re Rasmussen* 650 F.2d 12,12 1214, 211 USPQ 323, 326-327 (CCPA, 1981). See, also, M.P.E.P. § 2163.

In the case of this invention, the application provides methods that are straight forward and routine for (a) producing human sequence antibodies that specifically bind CTLA-4; and (b) screening those antibodies for particular properties, such as an ability to block B7 ligand, cross-reactivity with various tissues, and/or binding to CTLA-4 from other species of organism. Hence, in this instance description of the 10D1 antibody, coupled with the other disclosure in this application, is certainly sufficient for one skilled in the art to recognize that Applicants were in possession of the necessary common attributes or features possessed by members of the claimed genus.

For all of the above reasons, Applicants respectfully request that the claim rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

#### **VI. The Prior Art Rejections Should Be Withdrawn**

Claims 69-74, 77, 80-85, 88, 91-95 and 147 have been rejected under 35 U.S.C. § 102(a) as anticipated by International Patent Publication No. WO 00/37504 by Hanson *et al.* (hereinafter referred to as “Hanson”). In addition, claims 91-92 and 94-95 have been rejected under 35 U.S.C. §§ 102(e) and 102(a) as anticipated by U.S. Patent No. 6,051,227 by Allison *et al.* (hereinafter referred to as “Allison”), and also under 35 U.S.C. § 103(a) as being obvious over Allison in view of U.S. Patent No. 6,075,181 by Kucherlapati *et al.* (hereinafter referred to as “Kucherlapati”). Each of these rejections is addressed, in turn, below.

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With respect, first, to the rejections over the Hanson reference, Applicants understand this rejection to be premised on the Examiner's refusal to give pending claims in this application the benefit of their August 24, 1999 priority date (*i.e.*, the filing date of provisional application Serial No. 60/150,452). As explained above, however, the pending claims in this application are adequately described and supported in that provisional application and should therefore be accorded its earlier priority date. Hanson did not publish until June 29, 2000 and after the provisional application's filing date. Hence, Hanson is not available as prior art against the present invention. For this reason, Applicants respectfully submit that the rejection of claims as anticipated by Hanson should be withdrawn.


Turning, next, to the rejections of claims 91-95 and 147 as either anticipated by or obvious over the Allison patent, Applicants respectfully point out that these claims have been canceled in the above amendments, without prejudice or admission by Applicants. It is therefore believed that the prior art rejections of those claims have now been obviated.

For all of these reasons, Applicants respectfully submit that the prior art rejections of the pending claims should all be withdrawn.

## **VII. Conclusion**

Applicants note, with appreciation, that the Examiner has found claims 118-121, 124 and 130-133 to be allowable. It is further noted (also with appreciation) that the Examiner has indicated claims 115-117 and 122-123 would be allowable upon the correction of minor informalities that are noted in the Office Action. Those claims have been amended to correct the particular informalities, as explained above. Claims 91-95 and 147 have been canceled in the above amendments without prejudice or admission. Of the remaining claims, it is believed that the above remarks overcome each of the Examiner's rejections of those claims. Consequently, all of the pending claims in this

application are believed to be in condition for allowance. Entry and consideration of these amendments and remarks are therefore respectfully requested. An allowance is earnestly sought.

Respectfully submitted,  
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